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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference L 15-17106.2/me	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 02/04690	International filing date *(day/month/year)* 08.11.2002	Priority date *(day/month/year)* 17.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/18		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.05.2003	20.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Markopoulos, E Telephone No. +49 89 2399-8658

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/04690

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-21 as originally filed

Claims, Numbers

1-18 received on 05.08.2004 with letter of 02.08.2004

Drawings, Sheets

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

   see separate sheet

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Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US-A-4 992 419 (GRUBER WERNER ET AL) 12 February 1991 (1991-02-12)

D2: EP-A-0 528 314 (BOEHRINGER MANNHEIM GMBH) 24 February 1993 (1993-02-24)

D3: US-A-4 647 454 (CYMBALISTA SAMUEL) 3 March 1987 (1987-03-03)

D4: EP-A-0 909 564 (CHUGAI PHARMACEUTICAL CO LTD) 21 April 1999 (1999-04-21)

D5: WANG Y-C J ET AL: "PARENTERAL FORMULATIONS OF PROTEINS AND PEPTIDES: STABILITY AND STABILIZERS" JOURNAL OF PARENTERAL SCIENCE AND TECHNOLOGY, XX, XX, vol. 42, no. 2S, 1988, pages S04-S26, XP000984636 ISSN: 0279-7976

2. Novelty

D1 claims stabilized erythropoietin preparations containing physiologically compatible buffers such as phosphate buffer (pH 6.5 to 7.4 and especially 7.0 to 7.2), urea as main stabilizer, amino acids, and optionally PVP (Kollidon 12 PF) and isotonia-adjusting agents such as sodium chloride (col. 2, par. 6-7; example 6, table I; claims). D1 is no more novelty-destroying for claims 1-18 since urea and its use as stabilizer is excluded by the wording of new claims 1 and 16.

D2 claims a process for production of pharmaceutical preparations containing isolated or recombinantly produced human proteins namely EPO or G-CSF for infusion or injection purposes whereby conventional pharmaceutical auxiliary substances such as polyvinylpyrrolidone may be in the preparation having a pH-value from 6 to 7.4 especially 7.0 to 7.2 (claims 1, 3, 11; p. 3, l. 53 - p. 4, l. 54; examples 1 and 2). Since the independent claims have been restricted to specific constituents being present in the EPO composition, novelty can be acknowledged in view of D2.

Hence, the present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 is new in the sense of Article 33(2) PCT.

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3. Inventive step

D3 discloses stable interferon beta compositions whereby they are effectively stabilized by means of vinyl pyrrolidone polymer PVP used in a concentration of 0.5 to 10% wt/volume. The preferred molecular weight is 50,000 but can be also lower or higher (col. 1, par. 4, 7).

D4 discloses an erythropoietin solution preparation free from human serum albumin and purified gelatin, and preferably free from urea. Especially the necessity for human serum albumin being a blood product relying on donated blood for its supply has been questioned. The preparation contains amino acids as stabilizers as well as sodium chloride and phosphate and/or citrate buffer (claims 1,13,15; p. 2, par. 4-7; p.3, par. 8).

D5 reviews possible stabilizers in parenteral formulations of proteins and peptides e.g. erythropoietin (p. S4, col. 1, table) and also mentions PVP as stabilizer (p. S20, col. 1, par. 3).

D1, which is considered to represent the most relevant state of the art, discloses an erythropoietin preparation from which the subject-matter of claims 1-18 differs in that urea is used mandatorally as stabilizer.

The problem to be solved by the present invention may be regarded as finding an alternative to D1 for preparing stable erythropoietin solutions especially without needing to add human blood products such as albumin due to a certain risk of infection.

The solution proposed in claims 1-18 of the present application seems to involve an inventive step (Article 33(3) PCT) for the following reasons.

D1 as well as D3 use PVP as stabilizing agent for peptides with the difference that D1 also contains urea as main stabilizer and D3 uses PVP as main stabilizer whereby D3 relates solely to interferon beta.
D4 outlines the need of not using albumin in an erythropoietin preparation in order to avoid the risk of viral contamination. The solution of D4 is the use of amino acids as stabilizers. By combining the given documents, the skilled in the art could have used PVP as a stabilizing agent for erythropoietin solutions, but not as sole stabilizer or together with a poloxamer. The skilled man would have been prompted to use amino acids (see D4) and/or urea (D1, D2), and to leave out human serum albumin.

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Hence, inventive step is acknowledgable.

4. For the assessment of the present claim 18 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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